Remarks / Arguments

Claims 1-6, 10-15, 19, and 20 are pending in this application. Claims 7-9 and 16-18 are canceled. Claims 1, 10-12, and 15 have been amended. No new matter has been added.

Abstract

The examiner has required applicants to provide an abstract. This has been done.

Objection to disclosure

The disclosure was objected to on the ground that examples 26 and 50 show a thiazoline ring rather than a thiazole ring for the heterocycle. Applicants respond that examples 26 and 50 are the same compound, the structure is consistent with the recited molecular weight, but this compound is not covered by the claims. Accordingly, it is deemed that the compound of examples 26 and 50 is surplusage. Examples 26 and 50 have been deleted from the sheets of table shown on pages 30 and 32 respectively.

Rejection under §112, second paragraph

Claims 1, 4-6, 10-15, 19, and 20 were rejected under §112, second paragraph, on grounds of indefiniteness.

The examiner's recommendation that in the definition of R^6 on page 4 of claim 1 of the preliminary amendment should be deleted and replaced by a comma has been implemented in this amendment.

The examiner commented that the nature of the optional substituents for the NR^5R^6 rings recited at the end of claim 1 does not appear to be given. This language has now been deleted from claims 1, 10, 11, and 12.

Rejection under §112, first paragraph

Claims 1, 4-6, 10-15, 19, and 20 were rejected under §112, first paragraph, on grounds of lack of enablement for the scope of the aromatic heterocycles recited in the main claims in the definition of R^6. Claims 1 and 10 have now been amended to delete the language in the

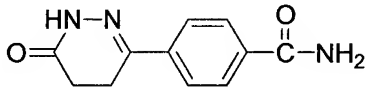
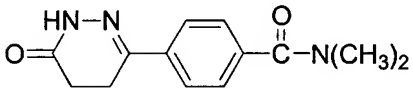
definition of R^6 which recited a 5- to 7-membered aromatic heterocycle having up to 3 heteroatoms selected from the group consisting of S, N, and O. In place of this language, the claims now recite the 5 heteroaromatic groups disclosed as preferred on page 9, lines 6 – 7 of the specification.

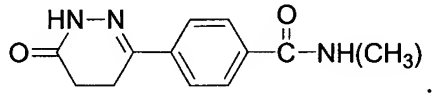
Other

Claim 15 has been corrected to clarify that the anemia results from individuals donating their own blood, and the treatment is to stimulate erythropoeisis. Reference to original claim 15 will confirm the correctness of this amendment.

Rejection under §103

Claims 1-6 were rejected under §103 as being unpatentable over Curran in view of March. Curran is employed for its disclosure of prior art compounds, while March is employed for its teaching of chemical reactions for the preparation of claimed compounds.

The examiner points out that the Curran J. Med. Chem. article discloses as example 18 the compound  . She states that the applicants' closest compound is  , and argues that this is an obvious variant of the Curran compound "since compounds which differ only in having H vs alkyl on a nitrogen are not deemed patentably distinct absent evidence of superior, unexpected results", referring to the cases In re Doebel and Ex parte Weston.

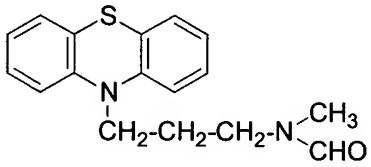
It appears that the examiner is mistaken in stating that the applicants' closest compound is that shown above, which is not exemplified in the present application. Example 14 of the present application discloses the compound  .

The examiner cites the decisions In re Doebel and Ex Parte Weston in support of her conclusion that "compounds that differ only in having H vs alkyl on a nitrogen are not deemed patentably distinct absent evidence of superior, unexpected results."

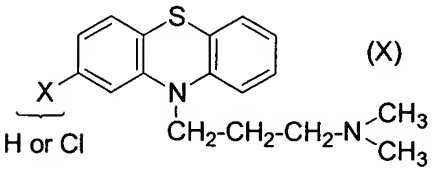
The Doebel and Weston decisions deal with the question of patentability of compounds which differ from prior art compounds by having a methyl group attached to an amino nitrogen rather than having a hydrogen on the nitrogen atom. They do not stand for the broad proposition stated by the examiner.

In re Doebel and Ex Parte Weston

In Doebel, the court determined that the rejection of the claimed compound

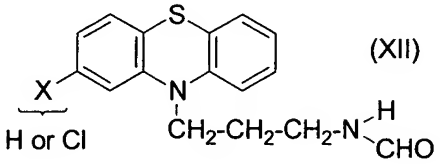


was based upon the structural similarity of this compound to the two prior art compounds



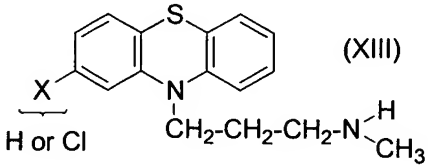
(X)

and

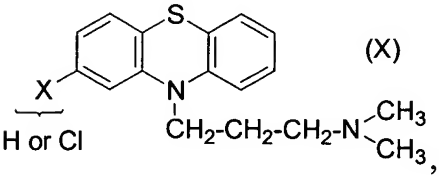


(XII) of Fujii in which the group X was H.

Also of record was the Brune reference, which disclosed that the desmonomethyl compounds of Fujii



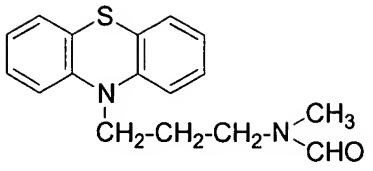
(XIII) had the same utility as the known Fujii compounds (X)



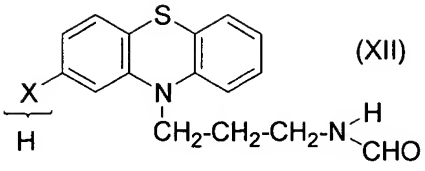
(X), but with decreased potency.

The examiner in Doebel argued in part that the claimed compound was a homolog of Fujii compound (XII) in which X was H, and that as (XII) is an intermediate in the synthesis of compounds (X) and (XIII), (XII) would be expected to have some of the same properties of the final products. By implication, he was arguing that the claimed compound was expected to possess the tranquilizing properties of Fujii compounds (X) and (XIII). He also argued that the claimed compound was similar to Fujii compounds (X).

The applicants submitted comparative test data regarding the claimed compound

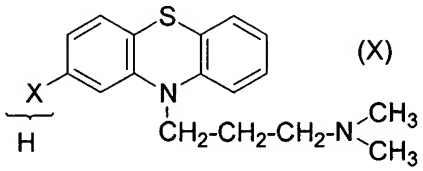


and Fujii compound (XII)



(XII)

but did not attempt to overcome the rejection of the claimed compound in view of the Fujii compound (X),

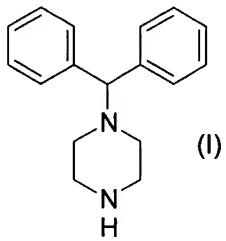


(X)

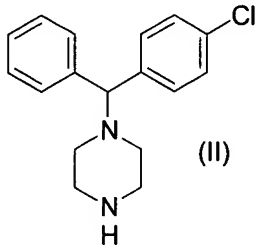
either by argument or by submission of comparative test data. The appeals court upheld the rejection on the ground that the applicants had responded to one aspect of the rejection, but not to both.

This decision does not stand for the proposition that "compounds that differ only in having H vs alkyl on a nitrogen are not deemed patentably distinct absent evidence of superior, unexpected results" as stated by the examiner. The applicants in Doebel could have attempted to argue that the rejection was not well founded, but chose instead to present comparative test data in attempting to overcome it. The court did not address the question whether the rejection was well-founded because that issue was not before it. The court stated in its opinion "The sufficiency of the Rule 132 affidavit ..... has been one of the major points of dispute in this case. As we view this case, however, the determinative issue is what rejections are before us and not the sufficiency of the comparative evidence provided in the Rule 132 affidavit." The court upheld the rejection on the ground that the applicants had addressed only one of the two aspects of the rejection, and therefore, they had not overcome the rejection. The court did not hold that submission of comparative test data showing superior/unexpected results was required to overcome the rejection. Thus, this decision does not validate the examiner's conclusion, stated above.

In Weston, the applicants claimed two compounds, N-benzyhydryl piperazine (I) and N-(p-chlorobenzhydryl) piperazine (II), the structures of which are shown below.

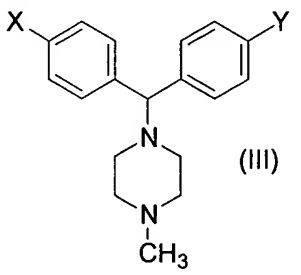


(I)



(II)

The claims were rejected as obvious over the disclosure of the Baltzly patent, US 2,630,435, which disclosed and claimed the corresponding N-methyl compounds, shown as (III).



(III) X and Y may be H, halogen, or CH_3

The examiner's ground of rejection in Weston was that the claimed compounds "are merely the next lower homolog of those of the reference and that as a matter of fact they are the obvious equivalents thereof."

The applicants argued that the claimed compounds could not properly be considered homologs of the Baltzly compounds because they did not have the same chemical properties, and they are capable of undergoing a whole series of reactions which the N-methyl-substituted nitrogen atom of the reference is incapable of undergoing.

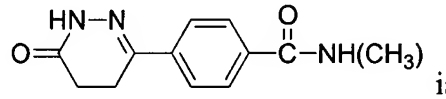
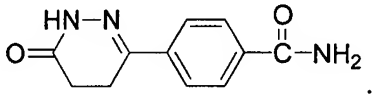
The applicants' original application had claimed benzhydryl piperazines in which the secondary nitrogen could bear H, (C_1-C_4)alkyl, or other groups. That application was involved in an interference with Baltzly, who won the N-methyl-substituted piperazines from the applicants and obtained his '435 patent.

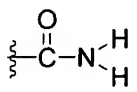
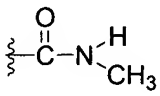
Under these facts, the applicants had both defined a series of homologous compounds, and admitted that for purposes of such compounds, H and lower alkyl groups were equivalent substituents on the lower nitrogen of the piperazine ring as shown in the formulae. This results from listing these groups in Markush language. The rejection of the claims was upheld on the ground that the applicants had admitted in their original application that the H and methyl groups were equivalent.

This decision does not stand for the proposition that "compounds that differ only in having H vs alkyl on a nitrogen are not deemed patentably distinct absent evidence of superior, unexpected results" as stated by the examiner. The decision does not address the questions whether, as a general proposition, replacement of a H on a nitrogen atom with a methyl group creates a homologous compound, or whether such a replacement should properly be considered prima facie obvious, or whether, if a prima facie obviousness rejection is made, it must be

overcome by submission of comparative test data showing superior unexpected results. This decision stands for the proposition that where the applicants have admitted that in a particular set of compounds a H and a methyl group on a nitrogen atom are equivalent, the NH-containing compounds will be held obvious in view of the N-methyl compounds. This decision does not validate the examiner's conclusion, stated above.

Arguments against the propriety of the prima facie obviousness rejection

First, it should be noted that the claimed compound  is not a homolog of the prior art compound  . Homologous compounds are members of a series of organic compounds in which each successive member has one more CH_2 group than the preceding member. Homology requires that there be a series of related compounds, and that the members of this series are necessarily the same sort of compounds. For example, CH_3OH, CH_3CH_2OH, $CH_3CH_2CH_2OH$, etc. are homologous compounds, because they constitute a series of compounds in which each succeeding member differs from the previous member by a CH_2 group, and they are all primary alcohols. However, CH_3OH, CH_3OCH_3, $CH_3OCH_2CH_3$, etc. are not homologous compounds despite the fact that each succeeding member of the series differs from the preceding member by CH_2, because all members of the series are not the same sort of compounds. In this example, the first member of the series is an alcohol but the remaining members are ethers.

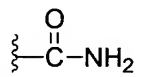
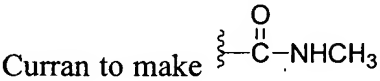
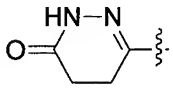
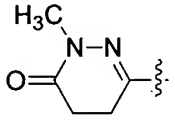
In the present case, there is no series of homologous compounds of which the claimed compound is a member, and the two compounds are not the same sort of materials. There is just a primary amide  and a secondary amide  . The applicants recognize that the nomenclature relating to homologs has become sloppy, sometimes referring to homologs as compounds which differ from one another by CH_2 (without recognizing the requirements for a series of compounds, and for the same sort of compounds). However, they do not acquiesce in such improper word usage.

The reason that homology is a quick route to a rejection for prima facie obviousness is that close homologs are generally understood to possess similar properties, so arguably, it would be logical that those skilled in the art would be led to make homologs of prior art materials in the expectation of obtaining new materials with properties similar to the prior art ones. This is not an absolute rule, however. There are circumstances in which homologous compounds would not be expected to possess similar properties, or in which they can be demonstrated not to possess similar properties, and in such cases, a prima facie obviousness rejection is improper. Furthermore, in cases in which the homologous compounds of the prior art series do not possess desirable properties or possess properties which are disadvantageous for the purposes of the prior art, it is clear that the prior art compounds cannot serve as a foundation for an obviousness rejection since they do not provide a suggestion that others should make similar compounds, and may in appropriate circumstances constitute a teaching away.

Second, where homology does not exist to provide a shortcut to establishment of an obviousness rejection, the examiner must apply the standard legal test for obviousness, namely, does the prior art taken together with the knowledge of one skilled in the art suggest making the change required to convert the prior art compound into the claimed compound, with the reasonable expectation that the compound so produced will possess the desired properties. The examiner has not applied this test in the present case. She has simply cited the Curran reference, pointed to example 18 of the reference, and concluded that the compound of the present application (presumably example 14) is an obvious variant of the unsubstituted compound of Curran "since compounds that differ only in having H vs alkyl on a nitrogen are not deemed patentably distinct absent evidence of superior, unexpected results".

The Curran reference states at page 277, first paragraph in the "biology" section, "Approximately 20 of the dihydropyridazinones described herein were active in the normotensive rat screen. The criteria for activity is that the mean arterial blood pressure (mm) must be $\leq$ 90 4 hr after dosing for two rats and $\leq$ 95 on retest (two rats) compared to an average value of 120 for untreated controls." Accordingly, since Curran's compound of example 18 is disclosed as exhibiting a hypotensive activity of MABP (mm) of 98, this compound is considered "inactive". Furthermore, the reference states at page 277, last paragraph of the "biology" section, "Unfortunately, preliminary toxicity experiments in several species including mice, dogs, and

monkeys revealed the presence of hemorrhagic patches in the heart area when the animals were treated with any of the active members of this series of compounds." Thus, there would not appear to be any reason why one of ordinary skill in the art would wish to make any derivatives of Curran's example 18. Compound 18 is considered by the author to be inactive as a hypotensive agent, and even if one were to make an active derivative, it appears that serious side effects would be expected. Indeed, the reference teaches away from the desirability of making any derivatives of example 18 of Curran. In view of these teachings of the Curran reference, it is deemed that there is no suggestion to make any derivatives of exemplary compound 18, and therefore, no suggestion that the compound of the present application should be made.

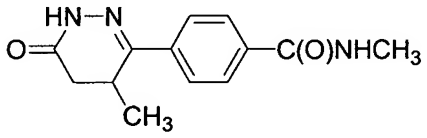
Third, for purposes of this argument only, if the examiner's statement that "compounds that differ only in having H vs alkyl on a nitrogen are not deemed patentably distinct absent evidence of superior, unexpected results" is accepted, then we are left with the question why the examiner chose to insert a CH_2 moiety into the N-H linkage of a primary amide group  of the prior art compound example 18 of Curran to make  , rather than choosing to insert the CH_2 moiety into the N-H linkage of the tetrahydropyridazine ring  of some other prior art compound to make  . The answer appears to be that none of the present applicants' exemplary structures possess a methyl group on that nitrogen atom of the ring. It is believed that the only way in which the examiner could have selected example 18 of the Curran article is by first focusing on the applicants' exemplary compound 14. This constitutes impermissible "hindsight reconstruction", which is not a proper basis for an obviousness rejection.

Accordingly, for the several reasons given above, the rejection of claims 1-4 and 6 for obviousness in view of the cited Curran and March references is deemed to be unfounded and improper, and its withdrawal s requested.

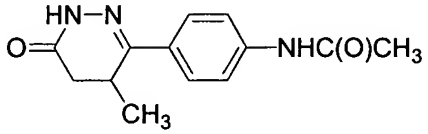
<u>The rejection of process claim 5 for obviousness</u>

With respect to the rejection of claim 5 on grounds of obviousness in view of the Curran and March references, the applicants respond first that the rejection of the claims to compounds has been dealt with above, and the compound claims are deemed to be patentable. Secondly, the law is now clear that a process of routine manipulative steps cannot be prima facie obvious when the material it uses or produces is patentable. See MPEP 2116.01, discussing the recent CAFC decisions In re Ochiai and In re Brouwer. Accordingly, assuming compliance with the requirements under §112, claim 5 should be patentable once the claimed compounds are found to be patentable.

The examiner commented with respect to the compound N-methyl-4-(4-methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)benzamide



which is discussed on page 7 of the specification and disclaimed from claim 1, that she could not find the species in the cited references or in a search of Chemical Abstracts, and asked for the applicants' comments. The undersigned has been informed that there appears to be an error in the application, and that this compound should not have been disclaimed. It is believed that the corresponding acylated aniline



was the compound of concern, but is not within the present claims. Accordingly, the disclaimer and related discussion have been deleted from page 7, the disclaimer has been deleted from pages 11 and 14 of the specification, and the disclaimer had been deleted from claim 1.

Patent Office personnel are informed that because a strike-through associated with certain numbers, a hyphen, or punctuation marks such as a comma, semicolon, colon, or period is difficult to see, in making amendments to certain of the claims, some language is deleted and re-inserted in order to clarify the amendments with respect to affected numbers or marks. Any such deletion/re-insertion does not affect the meaning or scope of the claim in which it occurs.

Similarly, because a strike-through of a single letter or a few letters of a word is difficult to see, when a word is to be modified, the entire word is deleted and the modified form of the word is re-introduced.

In view of the above amendments and arguments, this application is deemed to be in condition for allowance, and allowance is accordingly requested.

Respectfully submitted,

William F. Gray

Reg. No.: 31018
Phone: (203) 812-2712
Date: NOV 0 5 2003

William F. Gray
Bayer Pharmaceuticals Corporation
400 Morgan Lane
West Haven, CT 06516-4175